

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 June 2002 (20.06.2002)

PCT

(10) International Publication Number
WO 02/048165 A3

(51) International Patent Classification⁷: C07H 19/00,
19/207, C07D 307/88, C07F 9/655, A61K 31/70, 31/343,
31/665, A61P 35/00

(74) Agent: KNOWLES, Sherry, M.; King & Spalding, 191
Peachtree St., Atlanta, GA 30303-1763 (US).

(21) International Application Number: PCT/US01/49231

(22) International Filing Date:
17 December 2001 (17.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/256,066 15 December 2000 (15.12.2000) US

(71) Applicant (for all designated States except US): PHAR-
MASSET LTD. [BB/US]; 1860 Montreal Road, Tucker,
GA 30084 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): STUYVER, Lieven
[BE/US]; 3330 Forrest Bend Lane, Snellville, GA 30039
(US). PANKIEWICZ, Krzysztof, W. [US/US]; 3078
Clairmont Road, Apt. 538, Atlanta, GA 30329 (US).
PATTERSON, Steven [US/US]; 1501 Cimarron Park-
way, Dunwoody, GA 30350 (US). OTTO, Michael, J.
[US/US]; 1194 Staples Drive, Lilburn, GA 30047 (US).
WATANABE, Kyoichi, A. [JP/US]; 5765 Red Coat Run,
Stone Mountain, GA 30087 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
1 May 2003

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 02/048165 A3

(54) Title: ANTIVIRAL AGENTS FOR TREATMENT OF FLAVIVIRIDAE INFECTIONS

(57) Abstract: The disclosed invention is a composition for and a method of treating *Flaviviridae* (Hepacivirus, Flavivirus, Pestivirus) infections, including BVDV and HCV, and abnormal cellular proliferation in a host, including animals, and especially humans, using a small molecule or its pharmaceutically acceptable salt or prodrug.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H19/00 C07H19/207 C07D307/88 C07F9/655 A61K31/70
A61K31/343 A61K31/665 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 29331 A (SLOAN KETTERING INST CANCER ;UNIV ROCHESTER (US)) 22 December 1994 (1994-12-22) claims 1-3,8,11,22 --- -/--	1,2,8,9, 15,16, 36,37, 43,44, 50,51, 60-63,68



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 April 2002

Date of mailing of the international search report

23. 07 2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fitz, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 15563 A (CODON PHARMACEUTICALS INC) 16 April 1998 (1998-04-16)</p> <p>page 98, line 19; page 99, lines 1,19; page 100, lines 26,29,32; page 101, line 3; page 105, line 17; page 106, lines 1,17; page 107, lines 10-21; page 23, lines 19-29; page 3, lines 5-19</p> <p>---</p>	<p>1,2,8,9, 15,16, 36,37, 43,44, 50,51, 60-63,68</p>
X	<p>US 5 658 890 A (PANKIEWICZ KRYSZTOF W ET AL) 19 August 1997 (1997-08-19)</p> <p>examples 1,2,7,8; column 2, lines 29-64</p> <p>---</p>	<p>1,2,8,9, 15,16, 36,37, 43,44, 50,51, 60-63,68</p>
X	<p>LESIAK K ET AL: "SYNTHESIS OF NONHYDROLYZABLE ANALOGUES OF THIAZOLE-4-CARBOXAMIDE AND BENZAMIDE ADENINE DINUCLEOTIDE CONTAINING FLUORINE ATOM AT THE C2' OF ADENINE NUCLEOSIDE: INDUCTION OF K562 DIFFERENTIATION AND INOSINE MONOPHOSPHATE DEHYDROGENASE INHIBITORY ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 40, 1997, pages 2533-2538, XP002920574 ISSN: 0022-2623 page 2534, compounds 10-12; page 2533, columns 1 and 2</p> <p>---</p>	<p>1,2,8,9, 15,16, 36,37, 43,44, 50,51, 60-63,68</p>
X	<p>WO 98 34942 A (INSPIRE PHARMACEUTICALS INC ;RIDEOUT JANET L (US); PENDERGAST WILL) 13 August 1998 (1998-08-13) page 4, Table 1, Ac2C-NAD, Ac2C-PAD, Ap2BAD; page 7, lines 5-14</p> <p>---</p>	<p>1,8,15</p>
X	<p>RILEY T A: "SYNTHESIS OF 2.-(BETA-D.RIBOFURANOSYL) PYRIMIDINES, A NEW CLASS OF C-NUCLEOSIDES" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 24, 1 July 1987 (1987-07-01), pages 955-964, XP000575823 ISSN: 0022-152X page 958, compound 20</p> <p>---</p>	<p>1</p>

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 4 748 173 A (NELSON PETER H. ET AL) 31 May 1988 (1988-05-31)</p> <p>abstract; claim 1 -----</p>	<p>1,8,15, 22,29, 36,43, 51-55, 60-63</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/49231

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 22-53,56-68 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63,68 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63, 68 partially

Dinucleoside diphosphate derivatives of formula I, claim 1, wherein R is a nucleoside analogue with a 6-membered heterocycle as defined in formulae II and III; pharmaceutical compositions containing them; uses thereof.

2. Claims: 1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63, 68 partially

Nucleoside diphosphate derivatives of formula I, claim 1, wherein R is a mycophenol derivative with a sidechain of at least 3 C-atoms as defined in formula IV; pharmaceutical compositions containing them; uses thereof.

3. Claims: 3,10,17,24,31,38,45,56-59, 64-67 completely; claims 1,2,8,9,15,16,22,23,29,30, 36,37,43,44,50-55,60-63,68 partially

Nucleoside diphosphate derivatives of formula I, claim 1, wherein R is a mycophenol derivative with a C2-sidechain as defined in formula V; pharmaceutical compositions containing them; uses thereof.

4. Claims: 2,9,16,23,30,37,44,50-55,60-63,68 partially

Thiazofurin derivatives as defined in claim 2; pharmaceutical compositions containing them; uses thereof.

5. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

Derivatives of mycophenolic alcohols, aldehydes and acids with a C2-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

6. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

Derivatives of mycophenolic alcohols, aldehydes and acids with a C4-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

7. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Derivatives of mycophenolic alcohols, aldehydes and acids with a C6-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

8. Claims: 5,12,19,26,33,40,47,50-55,60-63,68 partially

Mycophenolic phosphates, phosphonates and sulfonates with a C2-sidechain as defined in claim 5; pharmaceutical compositions containing them; uses thereof.

9. Claims: 5,12,19,26,33,40,47,50-55,60-63,68 partially

Mycophenolic phosphates, phosphonates and sulfonates with a C2-sidechain as defined in claim 5; pharmaceutical compositions containing them; uses thereof.

10. Claims: 6,13,20,27,34,41,48 completely; claims 50-55, 60-63,68 partially

Mycophenolic hydrocarbyl derivatives as defined in claim 6; pharmaceutical compositions containing them; uses thereof.

11. Claims: 7,14,21,28,35,42,49-55,60-63,68 partially

Derivatives of mycophenolic diphosphates with a C2-sidechain as defined in claim 7; pharmaceutical compositions containing them; uses thereof.

12. Claims: 7,14,21,28,35,42,49-55,60-63,68 partially

Derivatives of mycophenolic diphosphates with a C4-sidechain as defined in claim 7; pharmaceutical compositions containing them; uses thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9429331	A	22-12-1994	US 5569650 A	29-10-1996
			AU 7171794 A	03-01-1995
			WO 9429331 A1	22-12-1994
			US 5658890 A	19-08-1997
			US 5700786 A	23-12-1997

WO 9815563	A	16-04-1998	AU 4815197 A	05-05-1998
			BR 9712285 A	20-11-2001
			CN 1239964 A	29-12-1999
			EP 0934325 A1	11-08-1999
			JP 2001501952 T	13-02-2001
			WO 9815563 A1	16-04-1998
			US 6326490 B1	04-12-2001

US 5658890	A	19-08-1997	US 5569650 A	29-10-1996
			AU 7171794 A	03-01-1995
			WO 9429331 A1	22-12-1994
			US 5700786 A	23-12-1997

WO 9834942	A	13-08-1998	US 5900407 A	04-05-1999
			US 5837861 A	17-11-1998
			AU 735684 B2	12-07-2001
			AU 6324198 A	26-08-1998
			AU 738907 B2	27-09-2001
			AU 6324298 A	26-08-1998
			BR 9807169 A	06-06-2000
			BR 9809562 A	02-10-2001
			CN 1292795 T	25-04-2001
			CN 1250369 T	12-04-2000
			EP 1003474 A1	31-05-2000
			EP 0981534 A2	01-03-2000
			JP 2001504858 T	10-04-2001
			JP 2001526635 T	18-12-2001
			NO 993776 A	06-10-1999
			NO 993777 A	05-10-1999
			NZ 337225 A	28-03-2002
			NZ 337405 A	27-07-2001
			WO 9834593 A1	13-08-1998
			WO 9834942 A2	13-08-1998
			US 6348589 B1	19-02-2002
			ZA 9800979 A	19-02-1999
			US 2001031743 A1	18-10-2001
			ZA 9801073 A	19-02-1999

US 4748173	A	31-05-1988	US 4727069 A	23-02-1988
			US 4861776 A	29-08-1989
			US 5177072 A	05-01-1993
